PROBLEMS IN THE GENETICS OF EPILEPSY *

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In contrast to the unequivocal findings regarding specific monohybrid genetic mechanisms in the major psychoses, schizophrenia and manic depressive psychosis, extensive work in the sphere of epilepsy has not resulted in the same clear-cut conclusions. In fact, the findings of certain substantial studies are in such striking conflict that we are presented with a serious problem as to how they are to be reconciled.

A second problem confronting us in the light of the discrepant findings referred to is whether, and if so on what rational premise, genetic counselling can be given in this field. And finally there is the problem of considerations arising from the advances of neurosurgery and neuropathology encroaching on the preserves of the group of epilepsies hitherto designated 'idiopathic' and 'crytogenic', to say nothing of the refined subtleties of interpretation that have come with the use of electroencephalography.

Definition of 'Heredity' and 'Epilepsy'

To begin with, some definition of the term epilepsy, and the meaningful application of the concept of heredity to it, would seem to be essential. In this connection I quote from Kallmann and Sander:[1]

'For the practical purposes of genetic investigation, Jackson's interpretation of epilepsy as the tendency to recurring excessive neuronal discharges within the central nervous system still provides an acceptable working basis. His physiological definition remains useful despite many possible variations which may be found not only in the type and localization of convulsive discharges, but also in the nature of their precipitating agents (Penfield).'

The current concept of heredity is best defined as the transmission of a person's norm of reaction to certain constellations of his life conditions. Irrespective of the kind of stimulating causes required for the provocation of convulsions, epileptic disease should not be expected to be inherited as such. What is genotypically transmitted will merely express itself in a particular type of predisposition which may lead to an abnormal susceptibility to various forms of stimulation.

From a genetic point of view it is advisable, therefore, to distinguish:

(*1*) the innate capacity for reacting convulsively to drastically stimulating agents (such as electroconvulsive therapy), from

* Paper read at the 2nd Congress of the South African Genetic Society, 1 October 1962, Pretoria.

(*2*) the inherited ability to develop convulsive disease without unusual stimulation, and

(*3*) the inheritance of special genes producing specific cerebral lesions (e.g. hereditary tumour) which may be incidentally associated with convulsions.

The hereditary origin of the capacity for having any type of convulsion is demonstrated by the fact that this form of motor reaction is universally provided for in the structural organization of higher vertebrates, from amphibia to Man. In Man, moreover, it is a universally given pattern of response, achievable by some only as a reaction to such potent stimulation as electroconvulsive therapy, by others only under the influence of something less potent such as alcohol, and others, our known clinically active epileptics, under the influence of the stimuli of everyday life. The graded quality of this universally given mode of response leads Kallmann and Sander[1] to postulate the polygenic character of the underlying genetic mechanism.

Biological and Genetic Findings Concerning Epilepsy in Animals

Despite the universal existence of the epileptic mechanism in the range of animals already indicated, the relative prominence of the clonic *vis-a-vis* the tonic component increases as we ascend the scale from the fishes and amphibia to the primates and Man.

Examples of claims for genetic mechanisms in 'animal epilepsy' are those of Atkeson, Ibsen and Eldridge[2] for the operation of a dominant autosomal gene in cattle, and of Nachtsheim[3] of a specific recessive gene which has an expressivity of at least 70% and is allelic to the pigment-determining factor of the Viennese rabbit.

Genetic Studies of Epilepsy in Man — Conflicting Evidence

Radically conflicting evidence in the field of the genetics of epilepsy in Man comes from Conrad[4] (Germany) and Lennox and the Gibbses[5,6,7] (USA), on the one hand, stressing the importance of the hereditary factor, and from Alström[8] (Scandinavia), on the other hand, whose figures reduce the role of genetics in this sphere to the barest minimum.

The Points at Issue

What then are the points at issue within the camp of the geneticists in the sphere of epilepsy?

The work stressing the importance of the genetic factor comes, as has already been indicated, from two groups. In Conrad's comprehensive pioneer study the expectancy figures in consanguineous groups of patients diagnosed as idiopathic epilepsy were 4·0% for siblings, 4·3% for two-egg twins, and 86·0% for one-egg twins. The similarity of the figure for siblings and two-egg twins (categories which may be equated to hereditary equipment), and the extremely high concordance rate for one-egg twins with identical hereditary equipment, as between co-twins, are eloquent and cogent testimony to the operation of the genetic factor. Lennox and the Gibbses, using dysrhythmia in the EEG as their criterion of epilepsy, record the remarkable finding of 100% concordance in one-egg twins and 25% concordance in those of the two-egg variety — the ideal figure for a fully penetrant single dominant gene.

Then, in 1950, came the publication of work by Alström, based on a study of epileptic patients admitted during the years 1925 - 1940 to the neurological clinic of the Caroline Institute of the Serefimer Hospital, the only university clinic for neurology in Sweden at that time. Alström remarked that the patients came from all over the country, but that the urban population, especially that from the capital, was over-represented. At the same time he claimed that this sample was otherwise probably a more representative one for patients suffering from convulsive disorders than a sample taken from hospitals for the insane or from institutions for epileptics, with their selection of mentally affected patients. The investigation of his 897 index cases with their blood relations began in 1945 and ended in 1950.

Salient findings of this study were as follows: In the first place the expectancy figures for parents (1·3 ± 0·27%), for siblings (1·5 ± 0·25%), and for children (3·0 ± 0·93%) were not significantly higher than those in the general population. Secondly, families with epilepsy in members other than in the index case were lacking in the majority, (i.e. 92%) of cases. Thirdly, among the 16 pairs of twins of this study, two of which pairs were monozygotic, there was not a single case of concordance as to epilepsy.

Despite Alström's figures quoted above, which reveal no genetic factor in epilepsy, the examination of individual pedigrees in his series discloses, according to his own submission, a genetic factor — in fact a monohybrid mechanism — in approximately 1% (11 index cases belonging to 8 families in his sample of 897 index cases and their families). This is the type of genetic mechanism, it will be recollected, that Lennox and the Gibbses postulated as being operative in their series, but present throughout instead of in only 1% of cases.

MEADOWLANDS CLINIC STUDY

With a view to finding further evidence towards settling the dispute, Hurst, Reef and Sachs[9] undertook a study at the Meadowlands Clinic in the South Western Bantu townships of Johannesburg during the period September 1959 — March 1961. The advantage held out by this clinical material for a genetic study is the large sibship size — average 5·8, range 1 - 16.

The preliminary pilot study produced evidence along the following two lines:

1. The percentage of families showing one or more members exhibiting epilepsy in addition to the index case, for comparison with Alström's low figure cited above.

2. The types of genetic mechanism suggested in different pedigrees contained in our material.

With regard to the first point, our material shows an incidence of 13 out of 46 families, i.e. a figure of 28·3%* in contrast to Alström's 0·8%. Statistical computation shows this difference to be significant at the 0·1% level. Thus, even at this early stage, our study has afforded evidence on the side of Conrad and the Gibbses and Lennox on the importance of the genetic factor in epilepsy.

Turning to the second point, analysis of the 13 positive

* This figure is probably conservative, since cases 10 and 39 in Table I each had a relative whose psychosis may well have been epileptic in nature, and have not been included in our figure.

TABLE I. GENETIC STUDY OF 46 FAMILIES

Identification	*No. of sibs*	*Relatives affected*	*Probable type of genetic mechanism*
1. J.Ma.	4	Negative	
2. L.K.	15	Negative	
3. S.D.	0	Negative, inadequate history	
4. D.S.	2	Negative	
5. L.M.	2	Negative	
6. J.Q.	3	One of 5 children — 2 siblings and mother	Penetrant single dominant
7. P.D.	3	Negative	
8. T.L.	3	Negative	
9. I.M.	4	Negative	
10. M.M.	4	Negative, paternal uncle mentally disordered	
11. M.N.	4	Negative	
12. A.M.	6	Negative	
13. J.Mo.	6	Maternal great-aunt on her maternal side Maternal cousin on her paternal side	Irregular dominant
14. N.M.	3	Negative	
15. S.B.	4	Nephew (1 of 2 sons of an elder brother)	Irregular dominant or recessive
16. B.K.	3	Negative	
17. M.F.	7	1 sibling	Recessive or irregular dominant
18. M.P.	4	1 uncle and 1 of 5 paternal siblings	Recessive or irregular dominant
19. M.Z.	3	1 of 3 other male siblings	Recessive or irregular dominant
20. G.D.	7	Negative	
21. Ja.Mo.	7	Negative	
22. V.K.	7	Negative	
23. M.N.	3	Negative	
24. E.M.	2	Negative	
25. F.N.	5	Negative	
26. P.M.	5	Paternal grandmother	Recessive or irregular dominant
27. M.Z.	3	Mother, 1 of 4 sibs, and only female child	Penetrant single dominant
28. C.N.	7	Maternal aunt and 1 of 4 siblings	Recessive or irregular dominant
29. W.N.	5	Negative	
30. M.Nd.	6	Paternal uncle and 1 of 3 siblings	Recessive or irregular dominant
31. Jo.Mo.	4	Negative	
32. J.Mak.	4	Negative	
33. L.T.	9	Negative	
34. H.M.	4	Negative	
35. E1.M.	0	Negative	
36. P.T.	8	Negative	
37. Ru.M.	6	Sister and father	Penetrant single dominant
38. S.D.	0	Negative, poor history	
39. B.M.	0	Negative, paternal grandfather psychotic	
40. S.J.	8	1 negative (twin pair)	
41. N.Ng.	7	Negative	
42. D.G.	4	Negative	
43. G.N.	12	1 sister and another sister with confusional episodes	Recessive or irregular dominant
44. D.M.	4	Negative	
45. Jo.Mo.	4	1 sibling	Recessive or irregular dominant
46. P.M.	6	Negative	

pedigrees (of the 46) shows that 3 of these are strongly suggestive of a penetrant single dominant mechanism, 1 of irregular dominance, while the remaining 9 are equally compatible with irregular dominance or recessiveness, as indicated in Table I. A portion at least, therefore, of these results is in line with the thesis of single dominance of Lennox and the Gibbses, appearing also in the 0·8% of Alström's cases where a genetic mechanism was conceded by him.

METRAKOS' RESOLUTION OF THE DIFFICULTY

In his paper presented at the Second International Conference of Human Genetics, in Rome, J. D. Metrakos[10] resolved the problem in a most ingenious manner. On the basis of the EEGs of the parents and siblings of 211 probands and 112 controls he claimed that epilepsy of the centrencephalic type may be explained on the basis of a single dominant gene showing a variable penetrance with age — such that the penetrance is low at birth, rises rapidly to almost complete penetrance at the ages of 4 - 16 years, and declines gradually to almost no penetrance at all after the age of 40 years. Alström's work might well be re-examined in the light of this hypothesis to determine whether his low familial incidence of cases may be due to an unusually poor representation of cases in the 4 - 16 age range.

The reason why Metrakos' theory would appear to constitute such an advance is its own intrinsic merit, coupled with the untenability of any other hypothesis. If it were to be argued, for instance, that the discrepancy between Conrad's findings and those of Alström's is to be explained by a greater concentration of the genetic variety

of epilepsy in mental hospital cases, this is counteracted by a similar discrepancy between the findings of the Gibbses and Lennox and those of Alström, both of which are based on clinic samples.

Apart from Metrakos' findings, therefore, we should have to fall back on the hypothesis of differential geographical distribution of epilepsy with a heavy genetic loading.

CONCLUSIONS AS TO PRACTICAL OUTLOOK IN HEREDITY COUNSELLING

In conclusion, let us review problems 2 and 3 of our introduction in the light of our major genetic evidence and argument just considered.

Armed with our modern armamentarium of neurological and neurosurgical knowledge and techniques, including electroencephalography, we are in a better position than ever before to separate our patients into symptomatic and idiopathic varieties. It is clear, in the light of contemporary knowledge, that only the second category of patients, the idiopathic or cryptogenic, are readily susceptible to heredity counselling; and here we are in the fortunate position of offering to the enquirer a low empiric risk figure on the basis of which few clients would be deterred from further procreation.

In the light of this, despite any differences we may have with Alström on matters of detail, we surely have common ground with him in substituting what Aschner and Kallmann[11] characterize as moderate eugenic recommendations for the existing legal restrictions of marriages of Swedish persons afflicted with hereditary epilepsy. 'Following a thorough discussion of the medical, social and genealogical aspects of the disease', he offers 'an emphatic warning against rigid applications of this restrictive law, especially in persons of satisfactory moral and intellectual standards'.

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